

(19)  **Canadian  
Intellectual Property  
Office**

An Agency of  
Industry Canada

**Office de la Propriété  
Intellectuelle  
du Canada**

Un organisme  
d'Industrie Canada

(11) **CA 2 259 730**

(43) 18.07.2000

(13) **A1**

(12)

(21) **2 259 730**

(22) 18.01.1999

(51) Int. Cl.<sup>6</sup>: **A61K 031/195, A61J 003/10,  
A61K 009/22, A61K 047/38**

(71) **SHERMAN, Bernard Charles,  
50 Old Colony Road, WILLOWDALE, O1 (CA).**

(72) **SHERMAN, Bernard Charles (CA).**

(54) **PASTILLES A DEGAGEMENT PROLONGE CONTENANT DU CHLORHYDRATE DE BUPROPIONE**  
(54) **SUSTAINED RELEASE TABLETS CONTAINING BUPROPION HYDROCHLORIDE**

(57) **A sustained release tablet comprising  
bupropion hydrochloride and hydroxyethylcellulose.**

O P I C  
OFFICE DE LA PROPRIÉTÉ  
INTELLECTUELLE DU CANADA



C I P O  
CANADIAN INTELLECTUAL  
PROPERTY OFFICE

(12) (19) (CA) **Demande-Application**

(21) (A1) **2,259,730**  
(22) 1999/01/18  
(43) 2000/07/18

(72) SHERMAN, Bernard Charles, CA

(71) SHERMAN, Bernard Charles, CA

(51) Int.Cl.<sup>6</sup> A61K 31/195, A61K 47/38, A61K 9/22, A61J 3/10

(54) **PASTILLES A DEGAGEMENT PROLONGE CONTENANT DU  
CHLORHYDRATE DE BUPROPIONE**

(54) **SUSTAINED RELEASE TABLETS CONTAINING BUPROPION  
HYDROCHLORIDE**

(57) A sustained release tablet comprising bupropion hydrochloride and hydroxyethylcellulose.



Industrie Canada Industry Canada

CA 02259730 1999-01-18

**ABSTRACT**

5     A sustained release tablet comprising bupropion hydrochloride and  
hydroxyethylcellulose.

10

15

20

25

30

**SUSTAINED RELEASE TABLETS  
CONTAINING BUPROPION HYDROCHLORIDE**

**BACKGROUND OF THE INVENTION**

5

Bupropion hydrochloride is a well known antidepressant. It is sold in the United States by Glaxo-Wellcome Inc. as prompt release tablets under the tradename WELLBUTRIN® and sustained release tablets under the tradename WELLBUTRIN SR®.

10

Bupropion hydrochloride is known to be relatively unstable, such that tablets containing bupropion hydrochloride will degrade at an unacceptably high rate unless the tablets are made by a method or using ingredients which result in improved stability. U.S. patent 5358970 discloses stabilization of bupropion hydrochloride by including in the tablets a stabilizer selected from a specified group of acids.

15

U.S. patent 5427798 discloses that bupropion hydrochloride is advantageously administered as sustained release tablets and certain formulations for making such tablets are disclosed and claimed. The formulations disclosed and claimed all comprise hydroxypropyl methylcellulose as the agent for controlling the drug release rate. Wellbutrin SR® tablets sold in the United States appear to be made within the scope of the claims of U.S. patent 5427798.

20

25

U.S. patent 5427798 discloses that the dissolution rate of bupropion hydrochloride from the sustained release tablets disclosed therein is preferably as follows:

30

- i) Between about 20% and about 60% in 1 hour,
- ii) Between about 50% and about 95% in 4 hours, and
- iii) Not less than about 75% in 8 hours.

The test conditions and apparatus used to determine the dissolution rate are specified to be:

5

Apparatus: USP Rotating Paddle (Apparatus II)

Stirring Rate: 50 rpm

Medium: 900 mL of distilled water

Temperature: 37°C

10

All of the tablets in the examples in U.S. patent 5427798 comprise glycine hydrochloride as acidic stabilizer, in addition to the bupropion hydrochloride and hydroxypropyl methylcellulose; and in each example the process of manufacture includes the steps of dissolving the acidic stabilizer in water and using the resultant solution to wet-granulate a mixture of hydroxypropyl methylcellulose and microcrystalline cellulose.

15

Such a process has the disadvantage of requiring the use of water and requiring the steps of preparing the solution, using the solution to wet-granulate a mixture of powders, and drying the wet mass.

20

The object of the present invention is to enable production of stable sustained release tablets comprising bupropion hydrochloride, which do not require use of hydroxypropyl methylcellulose and can be made without requiring a wet-granulation process.

25

#### DESCRIPTION OF THE INVENTION

It has been found that inclusion of hydroxyethylcellulose in tablets comprising bupropion hydrochloride, along with an acidic stabilizer, enables the production of stable sustained release tablets having appropriate dissolution

30

rate, and that such tablets can be made without requiring a wet-granulation process.

5

Hydroxyethylcellulose (hereinafter referred to "HEC") is sold in the United States and elsewhere under the tradename Natrosol®. HEC is a hydroxyethyl ether of cellulose. The cellulose molecule is comprised of a chain of anhydroglucose units, each of which contains three hydroxyls capable of reaction. Hydroxyethyl groups can be introduced into the cellulose molecule by reacting with ethylene oxide at the hydroxyls in the cellulose chain. Further hydroxyethyl groups can be introduced by reacting with ethylene oxide at the hydroxyls at the end of hydroxyethyl groups that have previously been added.

15

The average number of moles of ethylene oxide that become attached to each anhydroglucose unit in cellulose in these two ways is called "moles of substituent combined" or "MS".

20 A preferred HEC is that having MS of 2.5. This is available under the tradename Natrosol 250®. Viscosity of a solution of HEC in water increases with increased molecule weight of the HEC. Natrosol 250® is available in various viscosity types as follows:

25

Viscosity in cps at 25°C at various concentrations in water

<u>Viscosity Type</u>	<u>1%</u>	<u>2%</u>	<u>5%</u>
250HH	3400-5000		
250H4	2600-3300		
250H	1500-2500		
30 250MH	800-1500		
250M		4500-6500	

Viscosity in cps at 25°C at various concentrations in water

	<u>Viscosity Type</u>	<u>1%</u>	<u>2%</u>	<u>5%</u>
5	250K		1500-2500	
	250G		150-400	
	250E		25-105	
	250J			150-400
	250L			75-150

10

Preferred viscosity types are those with viscosity of above about 800 cps in 1% aqueous solution. Most preferred is the type with viscosity of about 1500 to 2500 cps in 1% aqueous solution, which is available as Natrosol 250H®.

15

The amount of HEC per tablet will preferably be from about 10 to about 60 parts per part of bupropion hydrochloride by weight. The amount of HEC per tablet will be more preferably from about 20 to about 40 parts per part of bupropion hydrochloride by weight.

20

In addition to comprising bupropion hydrochloride and HEC, the sustained release tablets will preferably also comprise another ingredient as a binder to increase the hardness of the tablets when the mixture of ingredients is compressed into tablets on a tablet press. This binder will preferably be either microcrystalline cellulose or methylcellulose.

25

Methylcellulose is available in the United States and elsewhere under the tradename Methocel A®. Methocel A® is available in several different viscosity grades corresponding to different molecular weights.

30

The lowest available viscosity grade, corresponding to the lowest molecular weight, is sold as Methocel A15LV® which has a viscosity of 15 cps in 2%

aqueous solution at 25°C. This lowest viscosity grade is preferred for use in the present invention.

5

The tablets of the present invention will preferably also comprise an acidic stabilizer, which will preferably be sodium bisulfate.

10

The tablets will preferably also comprise a lubricant, such as, for example, magnesium stearate to avoid sticking to the tooling in the tableting process.

The tablets will optionally also comprise a glidant such as, for example, colloidal silicon dioxide.

15

The tablets will be made by mixing the ingredients and compressing the mixture into tablets on a tablet press as it has surprisingly been found that the use HEC enables the obtention of a tablet exhibiting adequate hardness and slower-release properties without the need to wet-granulate the mixture.

20

Preferably the mixture will be made by a simple dry mix process; that is to say, simply by mixing ingredients together in dry form, without the addition of water or another solvent and the subsequent removal of such solvent by drying.

25

If the dry mixture of ingredients does not flow well enough for direct tableting, then the mixture can be slugged or compacted and then ground up into granules. The granules can then be compressed into tablets with or without the addition of other ingredients.

30

After the tablets are made they can optionally be coated with a film coating.

The tablets of the present invention will preferably have the same dissolution profile as specified in U.S. patent 5427798. That is to say;



- i) Between about 20% and about 60% in 1 hour,  
ii) between about 50% and about 95% in 4 hours, and  
5 iii) not less than about 75% in 8 hours.

The test conditions and apparatus used to determine dissolution rate are:

10 Apparatus : USP Rotating Paddle (Apparatus II)  
Stirring Rate : 50 rpm  
Medium : 900 mL of distilled water  
Temperature : 37°C

The following example is representative of the invention, but not limiting.

15

Ingredients were mixed in the relative amounts as follows:

Example 1

20	Bupropion Hydrochloride	100.0
	Natrosol 250H	32.0
	Methocel A15LV	80.0
	Sodium Bisulfate	5.0
	Magnesium Stearate	2.2
25	Colloidal Silicon Dioxide	<u>0.8</u>
		220.0

30

CA 02259730 1999-01-18

7

5 The ingredients were mixed, the mixture was compacted, the compacted material was ground up into granules, and the granules were recompressed on a tablet press into tablets of net weight 220 mg each.

Each tablet thus contained 100 mg of bupropion hydrochloride. Sample tablets were tested for dissolution rate by the aforesaid method and the results were found to comply with the aforesaid specifications.

10

15

20

25

30

**WHAT IS CLAIMED IS:**

5        1.    A sustained release tablet comprising bupropion hydrochloride and hydroxyethylcellulose for which the dissolution profile complies with specifications as follows:

- 10            i)      Between about 20% and about 60% in 1 hour,  
              ii)      Between about 50% and about 95% in 4 hours, and  
              iii)     Not less than about 75% in 8 hours.

when tested using USP Rotating Paddle Apparatus, at a stirring rate of 50 rpm, using as medium 900 mL of distilled water at 37°C.

15

2.    A tablet of claim 1 wherein the amount of hydroxyethylcellulose per tablet is from about 10 to about 60 parts per part of bupropion hydrochloride by weight.

20       3.    A tablet of claim 1 wherein the amount of hydroxyethylcellulose per tablet is from about 20 to about 40 parts per part of bupropion hydrochloride by weight.

25       4.    A tablet according to Claim 2 or 3 wherein hydroxyethylcellulose has a viscosity of at least about 800 cps in 1% aqueous solution at 25°C.

5.    A tablet according to Claim 2 or 3 wherein hydroxethylcellulose has a viscosity of from about 1500 cps to about 2500 cps in 1% aqueous solution at 25°C.

30

6.    A tablet of any of claims 1 to 5 further comprising a binder.

CA 02259730 1999-01-18

9

7. A tablet of claim 6 wherein the binder is microcrystalline cellulose.
- 5 8. A tablet of claim 6 wherein the binder is methylcellulose.
9. A tablet of any of claims 1 to 8 further comprising an acidic stabilizer.
- 10 10. A tablet of claim 9 wherein the acidic stabilizer is sodium bisulfate.
11. A process of making a tablet of any of claims 1 to 10 which comprises the steps of mixing in dry form and compression into tablets, without the use of water or any other liquid for wet granulation.
- 15 12. A tablet of any of claims 1 to 10 when made by a process of claim 11.

20

25

30